PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Multi-centre, Randomised Trial to Investigate Early Nasal High Flow Therapy in Paediatric Acute Hypoxemic Respiratory Failure: A Protocol for a Randomised Controlled Trial A Paediatric Acute Respiratory Intervention Study (PARIS 2)
AUTHORS	Franklin, Donna; Shellshear, Deborah; Babl, Franz; Schlapbach, Luregn; Oakley, Ed; Borland, Meredith; Hoeppner, Tobias; George, Shane; Craig, Simon; Neutze, Jocelyn; Gangathimn, Vinay; Wildman, Mark; Acworth, Jason; McCay, Hamish; Wallace, Alex; Mattes, Joerg; Fraser, John; Moloney, Susan; Gavranich, John; Waugh, John; Hobbins, Sue; Fahy, Rose; Grew, Simon; Gannon, B; Gibbons, Kristen; Dalziel, Stuart; Schibler, Andreas

VERSION 1 – REVIEW

REVIEWER	Dan L. Stewart, MD University of Louisville School of Medicine Louisville, KY USA
REVIEW RETURNED	02-May-2019

GENERAL COMMENTS	Abstract: The authors should mention that the analysis will divide the groups into an obstruction group and non-obstruction group. Reactive airway disease often follows RSV infections, so will there be any testing for viral agents or bacteria? Will there be division into subgroups--a 1 year old is very different than a 4 yo? Also, it would seem appropriate to track medications, i.e. bronchodilators, steroids (inhaled or IV), antibiotics/antiviral treatments.

REVIEWER	Prakadeshwari Rajapreyar Medical College of Wisconsin/ Children's Hospital of Wisconsin, Milwaukee, Wisconsin, United States of America
REVIEW RETURNED	06-May-2019

GENERAL COMMENTS	This paper addresses a very important concept of RCT with HFNC in the AHRF population. I have attached some comments and clarifying questions to the manuscript and uploaded them. Additionally the authors should include objective clinical criteria to categorize patients as having failed the treatment arm/ control arm OR state this as a limitation. The escalation from NHF or oxygen seems a little arbitrary and the lack of objective criteria makes it difficult to make sense of failure of an arm. Overall, Kudos to the authors for their work on this project The reviewer also provided a marked copy with additional comments. Please contact the publisher for full details.

REVIEWER	Werther Brunow de Carvalho Full Professor of Pediatric Intensive Care/Neonatology of the Department of Pediatrics Faculty of Medicine - University of São Paulo - Brazil
REVIEW RETURNED	07-May-2019

GENERAL COMMENTS	This is an important and relevant protocol addressing an important issue. However there are some points that need clarification / development. 1- For the sake of clarity move “Definitions" to the beginning of methods just after "Study Design and Settings" 2- We missed mixed lung diseases among the exclusion criteria. How are you going to deal with this? 3- Apparently the randomization will be stratified and in blocks. Detail the size of the block or if there will be randomization of the block size 4- In "Interventions and protocol" there is the phrase "For children presenting with SpO2 between 85 to 89/91% inclusive ..." Is the interval 85 to 89 or 85 to 91%? This observation is the same for all other citations where there is no definite interval. 5- Also in "Interventions and protocol” there is the phrase "For children presenting with SpO2 <85% the FiO2 is immediately increased to achieve SpO2 ≥90 / 92%." It will be increased by how much and for how long? Please describe how the titration of FiO2 will be performed for all cases 6- In Figure 1, it appears that the possibility of not tolerating NHF, changing for standard therapy and then requiring scheduling for ICU or high dependency was not considered 7- Although the authors state that "The study design is only prescriptive for the oxygen delivery method. For all other respiratory management, the individual hospital internal protocols will be followed, including pharmacological management." the final outcome of an Acute Hypoxemic Respiratory Failure is hardly dependent solely on the oxygen delivery method, so establishing a protocol to deliver beta 2 or correct dehydration (which many of these children present upon arrival) among other things would be of paramount importance. 8- In "secondary outcomes" a- What event will be considered the beginning of oxygen therapy? b- What will be considered a change in oxygen therapy? c- What will be considered escalation? Can outcome two be an escalation? d- What will be considered a complication? 9-The tolerance level will be measured by a visual analog scale. Has this scale been validated? 10- The evaluation of the intensity of respiratory patient-comfort level will be performed one hour after the start of oxygen therapy and 4 to 48 hours later. This second interval is very long and the time in therapy itself will be a bias. So, standardize the measurement time in eg 12h, 24h, 36h, 48h 11- Who will answer these questionnaires (EQ5D-5L and PEDSql)? In what moments will they be applied? Which health conditions will be evaluated? Why has it not been cited among secondary outcomes at least since, considering the current trend of migrating to Value Based Health Care, where patient benefit is the most important outcome, would not the outcome of quality of life / QALY be more interesting than length of stay?

REVIEWER	Bhavi Patel Nicklaus Children's Hospital Miami, Florida, USA
REVIEW RETURNED	17-May-2019

GENERAL COMMENTS	This study and the outcomes it might provide answers to is an important one. The protocol of the study with the use of high flow and regular nasal cannula oxygen needs to be better detailed. The author states about the titration of the fio2 but doesn't provide details on how much to go up and how often to increase. Also the high flow liter titration might be important to address as well. Also technically the regular oxygen study doesn't provide 100% fio2 so that statement needs to be changes. Also there should be standardization of how the conditions are treated other than oxygen therapy use at each hospital in order to not have any confounding factors. The make of the high flow system should be listed. There needs to be a full discussion on limitations that should be added to the paper. Thank you for letting me review this protocol.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
Comment:
Abstract: The authors should mention that the analysis will divide the groups into an obstruction group and non-obstruction group. Reactive airway disease often follows RSV infections, so will there be any testing for viral agents or bacteria? Will there be division into subgroups--a 1 year old is very different than a 4 yo? Also, it would seem appropriate to track medications, i.e. bronchodilators, steroids (inhaled or IV), antibiotics/antiviral treatments.
Answer:
We have added into the Abstract section the stratification of the two subgroups – obstructive and non-obstructive. We also added within the manuscript and specifically in Table 2 the 2 groups.

We added a new section to report on all data capture, including medication and feeding, which is part of our existing protocol.

Reviewer 2
Comment:
Additionally the authors should include objective clinical criteria to categorize patients as having failed the treatment arm/ control arm OR state this as a limitation. The escalation from NHF or oxygen seems a little arbitrary and the lack of objective criteria makes it difficult to make sense of failure of an arm.
Answer:
We acknowledge the arbitrary nature of the escalation. Based on the previous high-flow study in bronchiolitis we experienced that only in 75% of the cases the clinicians were following fixed escalation criteria. In view of this bias, we suggest in the protocol, as mentioned in the outcome section, clinical guidance when we expect clinicians to escalate therapy. All participating hospitals are using an early warning tool that dictates hospital internal escalation and referral practice to intensive care. Hence the authors view is that the escalation definition should be driven by the current practice of the attending clinicians and not solely driven by a study protocol to allow more generalisable results. The suggested escalation trigger points are:
We have included objective clinical criteria to categorize patients as having failed the treatment arm/ control arm. They are as follows:

a) heart rate remains >160/min for longer than 2 hours
b) respiratory rate remains >45/min for longer than 2 hours
c) oxygen requirement in NHF therapy arm exceeds FiO2 > 40/50% (dependant on hospital standard policy) to maintain SpO2 ≥90/92% or oxygen requirement in control oxygen arm exceeds standard oxygen therapy (2 L/min by nasal prong, or 8L/min by face mask) to maintain SpO2 ≥90/92% (dependent on hospital policy)
d) the hospital internal Early Warning Tool (EWT) calls for medical review
Comment
Abstract:
This is a slightly narrow definition of AHRF in terms of the primary etiology. It is okay to ultilize this but with statement that this is the population this is restricted to.
Answer
We changed to:
During the initial phase, AHRF is a clinical syndrome defined for the purpose of this study by an oxygen requirement and caused by pneumonia, lower respiratory tract infections, asthma or bronchiolitis
Comment:
Inclusion criteria: Unclear to me if the cut off is 90 or 92?
Answer:
We clarified:
and an ongoing oxygen requirement (SpO2 <90/92%* in room air, dependent on hospital policy) at the time of randomisation – observe patient in room air for up to 10 mins if safe to do so to confirm eligibility
Comment:
Should also maybe include patients in status epilepticus / other patients who are unable to protect their airway (with no cough or gag)
Answer:
We consider these children should be covered by the exclusion criteria of low level of consciousness.
Comment:
Child protection
Answer:
In Australia and New Zealand this is the common term of children under the guardianship of the child protection services.
Comment:
It is not usually practice to decrease flow to allow feeding on NHF as long as work of breathing is controlled at certain institutes. If this approach is to be supported would expect the following data to be monitored and/ reported in their analysis as 1) tolerance by monitoring of work of breathing and 2) average time prior to initiation of NG/PO feeds. This specifically becomes important in patients in whom the progression of disease is unclear.
Answer:
Feeding on high-flow is covered in the section on feeding. We do support continuing feeding at the discretion of the clinician. We monitor specifically the tolerance and the physiological data as this is captured in the electronic medical records. The newly data section should satisfy this request. However, from a medico legal aspect we suggest to cease the high-flow during oral feeding, albeit we already know that in our pilot trial this was in most cases not adhered to (reflecting once more the clinical reality).

Reviewer 3
Comment:
For the sake of clarity move “Definitions" to the beginning of methods just after "Study Design and Settings"
Answer:
We have rearranged definition section as suggested.
Comment:
We missed mixed lung diseases among the exclusion criteria. How are you going to deal with this?
Answer:
Since we are only interested in the oxygen requirement, any mixed lung disease can be included as long the attending clinician deems the high-flow intervention as appropriate.
Comment:
Apparently the randomization will be stratified and in blocks. Detail the size of the block or if there will be randomization of the block size.
Answer:
The block size for this study is ten. We have added this in the manuscript.
Comment:
In "Interventions and protocol" there is the phrase "For children presenting with SpO2 between 85 to 89/91% inclusive ..." Is the interval 85 to 89 or 85 to 91%? This observation is the same for all other citations where there is no definite interval.
Answer:
This range is dependent on participating site. If a site has a hospital policy to administer oxygen at a level of <92%, then the range is 85-91% and if a site has a level of 90%, then the range is 85-89%. We specified this more clearly in the section of the definitions.
Comment:
Also in "Interventions and protocol” there is the phrase "For children presenting with SpO2 <85% the FiO2 is immediately increased to achieve SpO2 ≥90 / 92%." It will be increased by how much and for how long? Please describe how the titration of FiO2 will be performed for all cases.

Answer:
The education for the titration of oxygen stipulates that the added oxygen is gradually increased until the acceptable threshold is achieved. We educate to increase it in 5% increments. We added in the manuscript:
For children presenting with SpO2 <85% the FiO2 is immediately increased in 5% increments to achieve SpO2 ≥90/92%.
Comment:
In Figure 1, it appears that the possibility of not tolerating NHF, changing for standard therapy and then requiring scheduling for ICU or high dependency was not considered.
Answer:
We believe that the diagram covers this flow path from NHF to standard oxygen (non-tolerance) therapy.
Question:
Although the authors state that "The study design is only prescriptive for the oxygen delivery method. For all other respiratory management, the individual hospital internal protocols will be followed, including pharmacological management." the final outcome of an Acute Hypoxemic Respiratory Failure is hardly dependent solely on the oxygen delivery method, so establishing a protocol to deliver beta 2 or correct dehydration (which many of these children present upon arrival) among other things would be of paramount importance.
Answer:
The strict protocolization of the non-oxygen therapy in these patients would be ideal and has been considered by the investigators. However the practicability of applying a cohesive protocol across 14

hospitals in very different health care settings rapidly became non-feasible. A restrictive protocol would also reduce the generalisability of the results.
Question:
In "secondary outcomes"
a- What event will be considered the beginning of oxygen therapy?
b- What will be considered a change in oxygen therapy?
c- What will be considered escalation? Can outcome two be an escalation?
d- What will be considered a complication?

Answer:
We specified more in detail in this section
a- Length of oxygen therapy since randomisation
b- Receiving a change in oxygen therapy in general ward settings from NHF to standard oxygen (non-tolerance) or from standard oxygen to NHF
c- Escalation of therapy such as non-invasive or invasive ventilation
d- Complications, serious adverse events (death before hospital discharge, cardiac arrest, pneumothorax or air leak syndrome

Comment:
The tolerance level will be measured by a visual analog scale. Has this scale been validated?
Answer:
The analogue scale is a well validated but crude tool in pain management and comfort level for ICU patients. However little validation for respiratory patients exists. Using more complex scoring systems have in our experience (PARIS trials) failed as most of the time was not being filled in.
Comment:
The evaluation of the intensity of respiratory patient-comfort level will be performed one hour after the start of oxygen therapy and 4 to 48 hours later. This second interval is very long and the time in therapy itself will be a bias. So, standardize the measurement time in eg 12h, 24h, 36h, 48h.
Answer:
Again the problem is the buy in factor by bedside nurses, which is unfortunately very poor in our settings as they are clinically very busy. However, we intend to use a general linear model for analysis, which allows for uneven intervals, however dependent in receiving in a high enough response rate.
Comment:
Who will answer these questionnaires (EQ5D-5L and PEDSql)? In what moments will they be applied? Which health conditions will be evaluated? Why has it not been cited among secondary outcomes at least since, considering the current trend of migrating to Value Based Health Care, where patient benefit is the most important outcome, would not the outcome of quality of life / QALY be more interesting than length of stay?
Answer:
The questionnaire will be filled in by parents as a proxy for the children.
We agree with the reviewer that a potential primary outcome could be value for care. The study is performed in public health care, hence the ‘consumer’ driven questions do exist but are lower rated in importance as there is no out of pocket or insurance payments required by the parents.

Reviewer 4:
Comment:
The protocol of the study with the use of high flow and regular nasal cannula oxygen needs to be better detailed.
Answer:
We believe that the present form of the protocol describes the use of the high flow. Most of the readers are familiar with the application of the prongs and use of the equipment.
Comment:
The author states about the titration of the fio2 but doesn't provide details on how much to go up and how often to increase.
Answer:
We purposely did not specify fixed increments as this leads to potential hypoxemia if the patient is not observed while titrating the oxygen to effect. Recent adult ICU data from Melbourne, Australia, showed that fixed protocols have the tendency to have patients spending too long in hyperoxic states.
Comment:
Also the high flow liter titration might be important to address as well.
Answer:
The flows are fixed per body weight and hence not titrated.
Comment:
Also technically the regular oxygen study doesn't provide 100% fio2 so that statement needs to be changes.
Answer:
We acknowledge that the application of pure oxygen does not provide 100% FiO2 if a maximum of 2L/min is delivered. We refer to 100% to pure oxygen.
Comment:
Also there should be standardization of how the conditions are treated other than oxygen therapy use at each hospital in order to not have any confounding factors.
Answer:
Similarly to Reviewer 3 we comment:
The strict protocolization of the non-oxygen therapy in these patients would be ideal and has been considered by the investigators. However the practicability of apply a cohesive protocol across 14 hospitals in very different health care settings rapidly became non-feasible. A restrictive protocol would also reduce the generalisability of the results
Comment:
The make of the high flow system should be listed.
Answer:
The equipment is mentioned in the ‘Intervention and protocol’:
NHF is set according to weight (Table 3) using the AIRVO-2 system (Fisher & Paykel Healthcare (FPH) New Zealand).
Comment:
There needs to be a full discussion on limitations that should be added to the paper.
Answer:
We have added a new paragraph:
The intervention of high-flow therapy cannot be blinded and a certain clinician driven bias may occur. The escalation of care is driven by clinical criteria and judgment and there is the potential bias to favour one intervention over the other. However, our previous high-flow trial in bronchiolitis showed that this element was not cofounding the study outcomes (22).

VERSION 2 – REVIEW

REVIEWER	Dan L. Stewart, MD University of Louisville SOM Louisville, KY 40202 USA
REVIEW RETURNED	26-Jun-2019

GENERAL COMMENTS	This version is markedly improved. 1. Suggest using the term limited-resourced countries. 2. Page 29--enrollment data needs updating.

REVIEWER	Prakadeshwai Rajapreyar Medical College of Wisconsin, Children's hospital of Wisconsin
REVIEW RETURNED	12-Aug-2019

GENERAL COMMENTS	Nice job, will be interesting to see what happens with the proposed feeding interventions

REVIEWER	Werther Brunow de Carvalho Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo
REVIEW RETURNED	17-Jul-2019

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.

REVIEWER	Bhavi Patel Nicklaus Children's Hospital Miami, FL, USA
REVIEW RETURNED	06-Jul-2019

GENERAL COMMENTS	This research protocol answers an important question. I have a few recommendations. 1. The protocol needs to be very specific so the study can be replicated. In the experimental arm of the high flow nasal cannula, it states that the HFNC should be started for spo2 <90/92% at 21% and can titrate up the fio2. But there has to be specific how when to titrate the fio2 and when to titrate up the flow. And exact amount of fio2 and flow at exactly what time increments. Also also who the patients show be weaned off the HFNC and supplemental oxygen. This way things are done similarly at all the centers participating in the study. 2. Please check for grammatical errors. Thank you.